How AstraZeneca's vaccine was hit by flawed trials, defects and politics — but might still save the world

Vaccine maker under pressure over clinical trial data and manufacturing problems

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As AstraZeneca's top managers held a virtual meeting on January 25, they were interrupted by breaking news. Germany's Handelsblatt newspaper reported that the company's Covid-19 vaccine — seen as one of the world's best hopes for conquering coronavirus — was largely ineffective in people aged over 65.

The shocked pharma executives scrambled to get in touch with their development partners at Oxford university before issuing an unusually emphatic denial: the claim was "completely incorrect".

Official data published several days later helped to further undermine the article, but its central assertion — attributed to German officials — was ominous evidence of worsening trouble with the EU.

Since mid-January when AstraZeneca told the pandemic-ravaged bloc it would be unable to deliver the expected volumes of vaccine, the relationship with the EU has been badly damaged. As it prepares to publish new data in the US, which is yet to approve the vaccine, the drugmaker also faces further scrutiny in the world's largest pharmaceutical market.

AstraZeneca must now defend itself against two separate charges: that its clinical trial data is weak and manufacturing inadequate. Meanwhile, the EU has found itself in the unusual position of demanding more of a vaccine that some member states believe may not work in the elderly.

An endeavour that started with impeccable intentions — to bring a low-cost vaccine to the world without profit — has harmed one of the pharmaceutical industry's star performers.

This account of a turbulent period for the Anglo-Swedish company is based on interviews with more than 30 executives, scientists and government officials in the UK, US and EU.

AstraZeneca is experienced in producing biologic medicines, but neither it nor Oxford had delivered a vaccine like this to market before © Vicenzo Pinto/AFP via Getty Images

An unconventional partner

As the pandemic raged in the spring of 2020, Oxford's scientists were working to bring a life-saving vaccine to the world at record speed. Needing a partner who could manufacture and distribute it, they auditioned some of the world's leading vaccine makers, according to people close to the talks.

Oxford wanted to distribute the vaccine to everyone, wherever they lived in the world. Early discussions with the UK's GlaxoSmithKline foundered and more advanced talks with Merck ended, too, on concern that the US drugmaker would not produce enough to supply the developing world and that the White House would not allow the UK to be supplied first. Merck said it has always made its vaccines and therapeutics available to people who need them around the world and its conversations with Oxford ended cordially in late April.

The Oxford scientists were ultimately sold on Pascal Soriot, AstraZeneca's urbane Parisian chief executive, whose ability to work almost round the clock through multiple time zones impresses fans and critics alike.

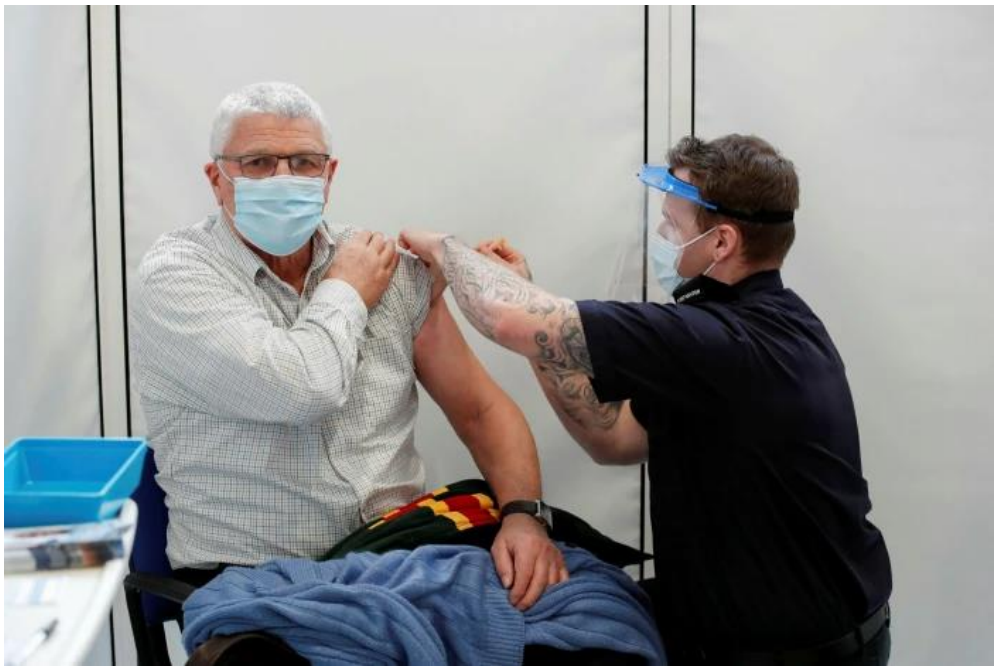
Yet although AstraZeneca is experienced in producing biologic medicines, it lacks its rivals' grounding in vaccines. Neither the company nor Oxford had ever delivered a vaccine like this to market before — let alone during a deadly pandemic.

Trial and error

Even before selecting their partner in April, the university scientists had made a head start — but took a route that would cause trouble later.

The scientists decided not to test the vaccine among large groups of over-65s, until they had plenty of evidence that it was safe in younger people. Andrew Pollard, director of the Oxford Vaccine Group, told the FT the decision was “cautious — and at the time, that was right”.

Almost a year later, however, the lack of data has led to many European countries advising against its use on older people. Emmanuel Macron, president of France, went further, saying — without producing evidence — that “everything points to thinking it is quasi-ineffective on people older than 65, some say those 60 years or older”.



Other vaccine makers realised regulators would want data on the older population, which is much more at risk of dying from Covid-19, and set up their trials accordingly.

When the first phase 3 trial analysis was published in November, it sowed confusion. AstraZeneca disclosed that the efficacy was highest among a subset of participants who had received half a dose before a second full dose; many of those had also received the second dose after an extended interval.

Scientists usually change one thing at a time to discern what is working — but here, cause and effect could not be untangled. In the subset, the vaccine was 90 per cent effective, but combined with other data, the scientists concluded it was 70 per cent effective overall.

The unorthodox data that shook some experts' confidence came after early manufacturing fumbles. Oxford was working with a contract manufacturer, which ended up making a half dose by accident. Then, when the scientists decided to test a two-dose course, they were hit by production delays, which meant a longer gap between doses as they waited for supplies.

According to Oxford's Pollard, this mistake has proved to be a blessing. "At that time, it felt like a frustration, but in retrospect it turned out to be extremely useful," he said. Later analysis showed it was probably the longer interval that made the vaccine more effective. This finding helped assure regulators that spacing out the two doses, as the UK has, would allow more people to be vaccinated with the bonus of added efficacy.

However, when AstraZeneca and Oxford revealed the data in November, they did not initially acknowledge their mistake, leaving the public to do its own detective work.

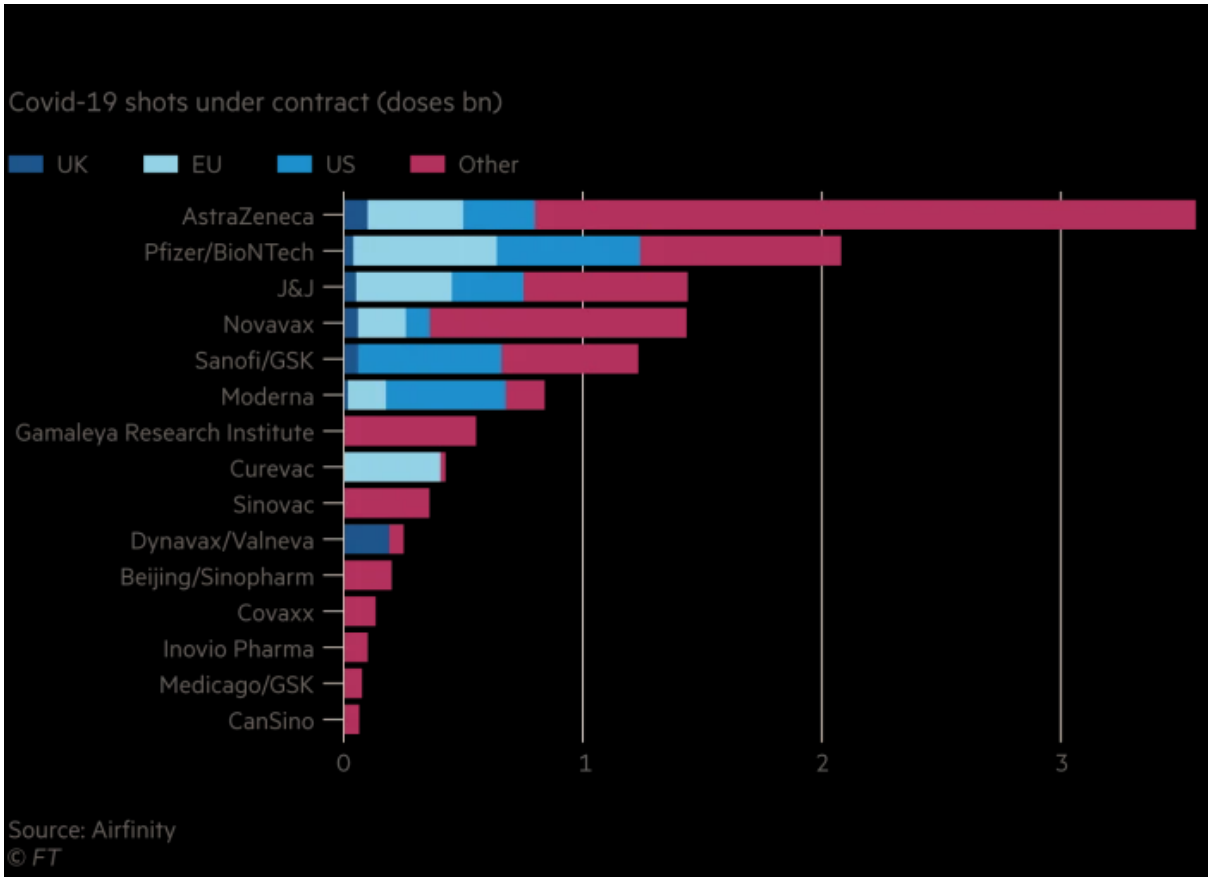
"It hadn't been war-gamed through from multiple perspectives. Instead, it was a very very narrow group who did it very, very quickly," one person familiar with the matter said.

In the UK, prime minister Boris Johnson exclaimed that the results from the UK drugmaker were "incredibly exciting". But the US response was more cautious. It was Moncef Slaoui, the Trump administration official in charge of the US government vaccine programme, who revealed that there had been fewer over-55s in the group which received the one-and-a-half dose regimen, potentially skewing the results further.

One industry executive put the different reception down to the UK government desiring a "national champion in post-Brexit Britain".

When surprisingly strong data from BioNTech/Pfizer and Moderna had landed earlier that month, their share prices jumped. But after its data was published, AstraZeneca's stock fell.

Eric Topol, director of the Scripps Research Translational Institute, part of a Californian hub for biosciences, said AstraZeneca's data stood out for the wrong reasons. "It was this hodgepodge, throwing all these different trials together and low dose, a standard dose, a dose by accident. I mean, you just can't make this stuff up," he said.



Uproar in Brussels

While the UK and the US struck a deal with AstraZeneca in May, the EU did not sign its contract until late August. The first indication of supply problems in Europe came in November when AstraZeneca realised the yield from one manufacturing site was substantially below what had been expected.

Hopes that subsequent batches would have higher yields were dashed; in a different plant some doses were lost because of contamination. Each lost batch would take 55 days to replace.

Some problems were identified not by the company but by regulators. During testing last month, the Dutch National Institute for Public Health and the Environment (RIVM) discovered that at least one batch contained less of an active ingredient than required, said people familiar with the matter.

In mid-January, AstraZeneca formally told the European Commission at a meeting attended by dozens of officials that it could not meet the original delivery schedules. Emotions ran high on both sides, said people involved.

The problems with the EU reflected in part a communication failure by the company, said bloc officials and diplomats. Another question is whether AstraZeneca sufficiently explained, and the EU sufficiently understood, the uncertainties inherent to vaccine making.

“With chemicals, you can mix things together and you know what you will get, whether it’s 200 grammes or 200 tonnes,” said one observer of the dispute from the industry side. “With biologics, it doesn’t work like that. I think the biology of it is completely overlooked by all sides.”

A mistake over dosing proved to be a blessing. The longer intervals between jabs made the vaccine more effective © Dhiraj Singh/Bloomberg

A senior member state diplomat said AstraZeneca had not been “sensitive enough to the crisis” gripping the EU as it tried to boost lagging vaccine rollout. They “surprised the commission” with the disclosure that the deliveries would not meet targets, the official added. Allies of the drugmaker disputed that, pointing to weekly appearances at meetings of the commission’s vaccines steering group.

At an emergency meeting, Soriot stood his ground, telling officials their criticism was unfounded and inaccurate and public attacks were not the way to build a relationship. “Soriot handled it really quite well,” said one person familiar with the encounter.

EU officials were particularly infuriated by AstraZeneca’s apparent suggestions that the EU and UK supply chains were separate. Soriot stressed that the company was obliged only to make its best efforts to stick to the initial delivery schedule. “It’s Davos man,” said one EU official of the chief executive’s performance. “These guys are never apologetic.”

Two days later, commission president Ursula von der Leyen said the company had agreed to provide 40m first-quarter doses instead of 31m — an improvement, but one that made up only 13 per cent of the gap to the 100m doses the EU was originally expecting. The company also announced that it would start delivering a week earlier than scheduled and expand manufacturing capacity in Europe.

Soriot has not been without internal critics in recent weeks. One person close to discussions said some AstraZeneca board members believed the situation in Europe should never have been allowed to deteriorate to the point of open warfare. They feared that, under pressure from the UK government and heavily focused on securing approval for his company's jab in the US, the chief executive may not have paid enough attention to what was happening in another vital region.

Sharpening the sense of resentment from the EU side is a belief that the UK, where the rollout of the vaccine has been one of the most successful in the world, has been granted preferential treatment.

While the tense talks with the commission have burst into public, there has been constant quiet high-level contact between the company and the UK government, said people familiar with the matter.

Both Johnson and the UK health secretary Matt Hancock have regular conversations with Soriot — "almost daily", according to some government insiders. Meanwhile, Oxford's Pollard has appeared alongside the UK prime minister at a Downing Street press conference.

Showing the closeness of the relationship, it was the Johnson government that alerted AstraZeneca to the fact the commission had accidentally published a poorly redacted version of its contract with the EU, which included sensitive pricing information.

UK officials do not dispute that they have a stronger relationship with AstraZeneca but — rather than warm and fuzzy patriotism — they put it down to early commitments and cold hard cash.

“We put a lot of money in manufacturing, co-funded the clinical trials with Oxford university,” said one senior official. “We were the first country to sign a deal with AstraZeneca, first to authorise and the first to deploy.”

The government was always confident AstraZeneca would honour its contract to supply 2m doses a week to the UK.

“Astra were rock solid because our contract is rock solid,” said one ally of Hancock. “It’s quite simple: we have an exclusivity contract with them and the EU don’t.”

US regulators reject UK data

If AstraZeneca’s relationship with the UK government is rock solid, in the US it is more like quicksand.

In May, the company signed up to Operation Warp Speed, the Trump administration’s programme to develop vaccines, saying it could deliver the first doses as early as October.

As then-president Donald Trump piled on political pressure to get an approval before the election, AstraZeneca spoke to the White House about bypassing the usual regulations. One plan was to approve it on the basis of the UK study of 10,000 people, even though the US scientific agencies had asked for 30,000, according to people familiar with the matter.

Had this plan worked, AstraZeneca would have been the first vaccine to be approved in the US — not, as it looks now, potentially the fourth.

When AstraZeneca's trial was forced to pause enrolment on a potential safety concern, the company pushed the US Food and Drug Administration to rely on the data it had, rather than waiting for a whole new clinical trial.

One US official briefed on the conversations said: "We were coming under a lot of pressure to allow the company to apply for authorisation using the data from the UK and elsewhere. But we simply had too many questions over that data."

Two officials told the FT they were concerned about the number of older people enrolled in the trials so far, and the confusion around the one-and-a-half dose regimen.

Former US president Donald Trump's Operation Warp Speed gave AstraZeneca and Oxford up to $1.2bn to support trials and manufacturing © Tasos Katopodis/Getty Images

One of those officials said Peter Marks, the chief vaccines regulator at the FDA, personally told AstraZeneca staff that they should complete their US trials before applying for emergency approval. Marks did not respond to a request for comment.

The FDA said: "In evaluating a request for an Emergency Use Authorisation, the FDA can consider foreign clinical trial data. However, sponsors should consult with FDA regarding the specific clinical data that they propose to support their EUA request."

Natalie Dean, a biostatistician at the University of Florida, said the FDA is looking for a "clear regimen", not the "confusing" data presented by AstraZeneca. If they did not ask for a new trial, she said, we would never have enough data to tell how well it works in the older population.

Warp Speed, which gave AstraZeneca and Oxford up to $1.2bn to support trials and manufacturing, also set conditions, emphasising enrolling older adults and people with comorbidities.

Now the US trial is fully enrolled, with data expected in the coming weeks. AstraZeneca is hoping for an emergency approval by April. Soriot has been busy talking to the US regulator, in meetings that one person close to the company described as “very constructive”. The data will be an important test not just for the US, but eagerly awaited by other countries wanting more information.

Oxford chose AstraZeneca because it was willing to pursue a moonshot: vaccinating the globe, while charging less than the price of a cup of coffee for each jab. But like a space mission, every small slip-up has been scrutinised by politicians and broadcast to billions.

The company may yet emerge as one of the heroes of the pandemic, responsible not only for preserving lives but allowing locked down economies to open faster. In that case, Soriot will be garlanded for his public spiritedness and foresight. But further missteps will bring more opprobrium. “It is the biggest vaccine supplier for the world,” said Topol of Scripps Research. “It just can’t mess it up.”

By Sarah Neville, Hannah Kuchler in New York, Kiran Stacey in Washington, Michael Peel in Brussels and Anna Gross, Sebastian Payne, Donato Paolo Mancini and George Parker in London